Dermal Absorption of Molinate, Napropamide, Permethrin, Dichlorvos, and Hydrogen Cyanamide in Rats

By

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HS-1791 May 12, 1999

California Environmental Protection Agency
Department of Pesticide Regulation
Worker Health and Safety Branch,
830 K Street, Sacramento
California 95814-3510

This technical report contains five memoranda with the following titles:

Oleta Melnicoe, Registration Specialist
Pesticide Registration Branch

March 29, 1991

Sacramento

Via: John Ross, Senior Toxicologist
Worker Health and Safety Branch

5-8474

-Tian Thongsinthusak, Staff Toxicologist
Worker Health and Safety Branch

PRODUCT NAME: Ordram^{R}
ACTIVE INGREDIENT: Molinate
COMPANY NAME: ICI Americas Inc.
I.D. NUMBER: RA-126893-E
DOCUMENT NUMBER: 228-099
EPA REGISTRATION NUMBER: 10182-0-
TITLE: Molinate/SB 950 Risk Assessment-Dermal Absorption Study in Rats
(Report No. CTL/C/2396, January 21, 1991.

The registrant has submitted a final report on the dermal absorption study of molinate in rats and a follow-up document on dose preparation (1). Worker Health and Safety Branch has reviewed both documents and determined the acceptability of the dermal absorption study to be used in the Department risk assessment process.

Approximately seven-week old male rats (Crl:CD(SD)BR strain) were used in the study. These rats were inspected, acclimatized, identified, and weighed accordingly. The body weight range of the rats was from 229 to 310 grams.

An area of the dorso-lumbar skin, was clipped free of hair using veterinary clippers. The skin was then washed with acetone. An area of 11.6 cm^2 was enclosed with a glass saddle, with an internal diameter of 3.85 cm, using Zap-A-Gap^{TM} adhesive. Rats were then placed individually in all-glass metabowls, which allowed separate collection of urine and feces.

Four dose groups used in this study were: aqueous dosing solution-0.1, 1, and 10 mg a.i./rat and 15% molinate on fines of Little Rock kaolin clay (w/w)-1 mg a.i./rat equivalent approximately to 8.6, 86, 860 and 86 ug a.i./cm^2 respectively. Four rats were used for each sacrifice time.

(^{14}C)-Molinate (specific activity of 135.3 uCi/mg and a purity of >99%) was mixed with non-labeled molinate for the preparation of administered doses. For aqueous dosing preparations, the lowest dose was prepared in deionized water; whereas, for 1 and 10 mg a.i./rat, the doses were prepared in 0.1% Tween 80 in deionized water (v/v) because of solubility problems. For 15% (w/w) formulation, labeled and non-labeled molinate were mixed with fines of Little Rock kaolin clay. No other formulation ingredients were apparently added to all doses. The prepared doses were then applied to the prepared site skin. Water was not added to the 15% (w/w) formulation preparation, nor was the dose site areas premoistened. A non-occlusive patch was used to cover the dosed area.

The patch, an activated charcoal filter resting between two glass sinters, was placed in the glass saddle to trap volatile portions of molinate.

Rats were sacrificed at the end of 4, 10, 24 hours (group 1-3) and 120 hours (group 4). Treated areas were not washed off for the first three groups; however, treated sites were washed at 10 hours after dosing for group 4. Urine and feces samples were collected at termination of the study for groups 1-3; whereas, for group 4, urine, feces, and cage washes were collected at the end of 10, 24, 48, 72, 96, and 120 hours. Other samples were also collected for the analysis, such as activated charcoal filter, treated skin, cage washes, and carcass. Results of this study are summarized in Table 1.

Table 1. Results of the dermal absorption study of molinate in male rats.

Dose (mg/rat)	Hours post-admin./	Percent administered dose 4	10	24	120
0.1 (Aq. Form.)	Bound skin residue	9.2	4.2	3.6	1.4
	Urine	5.2	10.5	25.2	35.5
	Feces	0.1	1.0	9.9	3.4
	Carcass	19.5	13.0	13.3	2.8
	Sub-total	34.0	28.7	52.0	43.1
	% Recovery	76.0	80.0	77.3	82.0
	% Dermal absorption[a]	44.7	35.9	67.3	52.6
1.0 (Aq. Form.)	Bound skin res.	7.0	6.4	3.2	1.0
	Urine	7.6	18.6	22.4	24.3
	Feces	0.6	1.1	2.4	1.5
	Carcass	18.3	17.5	8.3	2.2
	Sub-total	33.5	43.6	36.3	29.0
	% Recovery	91.7	86.5	89.7	83.8
	% Dermal abs.[a]	36.5	50.4	40.5	34.6
10 (Aq. Form.)	Bound skin res.	4.5	5.4	2.8	0.3
	Urine	2.4	17.6	27.2	28.0
	Feces	0.0	1.3	7.4	2.9
	Carcass	15.4	18.3	6.9	1.7
	Sub-total	22.3	42.6	44.3	32.9
	% Recovery	87.2	87.9	92.0	100.0
	% Dermal abs.[a]	25.6	48.5	48.2	32.9

Aq. Form. = Aqueous Formulation

Dose (mg/rat)	Hours post-admin./	Percent administered dose 4	10	24	120
	Bound skin res.	8.4	5.3	5.4	1.3
1.0	Urine	6.5	10.5	13.5	23.0
15% (w/w)	Feces	0.0	3.0	10.0	2.0
Formulation	Carcass	15.8	11.6	7.7	1.9
	Sub-total	30.7	30.4	36.6	28.2
	% Recovery	95.4	92.2	88.5	93.5
	% Dermal abs.[a]	32.2	33.0	41.4	30.2

[a] % Dermal absorption = (100 x sub-total)/% recovery

Plots of percent dose excreted (urine + feces) at the end of 10, 24, 48, 72, 96, and 120 hours indicated continued excretion of the applied dose with marked reduction of bound skin residues in all dose groups. Furthermore, percent of administered doses trapped in the activated charcoal filter remained relatively similar at the end of 4, 10, 24, and 120 hours; this revealed that the disappearance of bound skin residues was apparently not the result of volatilization. Therefore, from the above evidences it is reasonable to conclude that bound skin residue from the dosed skin area was bioavailable.

According to the report, inert ingredients that are incorporated in the commercial formulations were not added to administered doses for both aqueous and 15% (w/w) formulations. These ingredients should have been added according to the EPA guideline (2) to simulate the field exposure scenario. Further, water was not used to wet dosed skin sites or mix with the 15% (w/w) formulation dose before administration to rats; this may not represent the situation where workers normally sweat or have oily skin during loading. In contrast to this study, methanol was used as a solvent in a previous study (3), because molinate is miscible in methanol; dermal absorption was determined to be 56 percent (4, 5). Despite the differences in solvent used in the present study and the previous study, rat dermal absorption was remarkably similar suggesting that for molinate, solvent may not be the most significant factor in determining dermal absorption.

After a careful evaluation of the present study, a dermal absorption of 53 percent will be used for deriving the human dermal absorption estimate. The result was determined from the 0.1 mg/kg (8.6 ug/cm^2) dose group, which is considered in the similar range of worker exposure. This dermal absorption is similar to the mean dermal absorption (50%) from the same dose group for all four-sacrifice times. This dermal absorption also appears representative of the 15% (w/w) formulation dose group.

Recommendation

Dermal absorption of 53 percent will be used to derive human exposure estimates, unless the registrant elects to do a new study. However, the study protocol must be approved by the Department.

References

1. ICI Americas Inc. 1991. Molinate/SB950 Response: Preliminary dermal absorption study (HUK Report No. 6587-72-297/ICI Report No. CTL/C/2546).

2. Zendzian, Robert P. 1989. Skin penetration method suggested for Environmental Protection Agency requirements. J. Amer. Coll. Toxicol. 8(5): 829-835.

3. ICI Americas Inc. Percutaneous absorption of Ordram ^{14}C in male rats under occluded and unoccluded conditions. CDFA Pesticide Registration Document Number 228-083.

4. Fong, H.R. 1989. Molinate: Metabolic fate, dermal transport, and human exposure data (Appendix B). CDFA, Worker Health and Safety Branch.

5. Thongsinthusak, Tian. 1991. Percutaneous absorption of Ordram ^{14}C in male rats under occluded and unoccluded conditions. Memo, Worker Health and Safety Branch, February 21, 1991.

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(TCW/Dermal/Molin02)

Kathy Wynn, Registration Specialist
Pesticide Registration Branch

January 17, 1995

Sacramento

445-4267

-Tom Thongsinthusak, Staff Toxicologist
Worker Health and Safety Branch

PRODUCT NAME: Devrinol®
ACTIVE INGREDIENT: Napropamide
COMPANY NAME: ICI Americas Inc.
I.D. NUMBER: 136079-E
DOCUMENT NUMBER: 328-095
EPA REGISTRATION NUMBER: 10182-258-
TITLE: Dermal Absorption of Devrinol® in Rats

A dermal absorption study of Devrinol® 50-WP in male rats was conducted by Research Triangle Institute in October, 1987 and was completed in January, 1988. This study was conducted in compliance with EPA FIFRA Good Laboratory Practice standards as specified in 40 CFR, part 160. Various phases of the study were inspected by the quality assurance (QA) specialist of the QA Unit. The study director and the QA specialist signed the final report. A summary of this dermal absorption study and the evaluation of the results are presented below.

A. Test substances

Both labeled and unlabeled Devrinol® were used in the preparation of administered doses. The radiochemical purity of [naphthoxy-1-^{14}C] Devrinol® was determined to be >98% by a combination of HPLC and liquid scintillation spectrometry. This dermal absorption study was conducted using four different dilutions of Devrinol® in distilled, deionized water. For the preparation of the dose, Devrinol® 50-WP, a blank formulation (50-WP) and [^{14}C] Devrinol® in methanol were mixed and suspended in water. Four dose levels used in the study were 2686 (1 to 2 dilution), 192 (1 to 25 dilution), 88 (1 to 50 dilution), and 45 (1 to 100 dilution) μg Devrinol®/cm^2.

B. Preparation of Animals

Male CD rats [Crl: CD®(SD)BR] from Charles River Laboratories were used in the study. Body weights of these animals ranged from 224 to 258 g. Upon arrival these animals were examined by a veterinarian to be in good health. All animals were quarantined for a minimum of 7 days prior to the study. Four animals were used per sacrifice time for each dose. Approximately 24 hours prior to dosing, the animals were sedated with ketamine:xylazine (7:1, 60 mg/kg, IM) and the fur on their backs was removed by using animal clippers. The clipped area on each animal was washed with soapy water, then rinsed with water and dried. The dose area was defined by placing a 4.9 x 4.9 cm rectangular cardboard template in the center of the clipped area. An outline of the cardboard was made on the rat with a permanent type felt tip marker. A protective appliance, made of Reston® self-adhering foam pad, was attached to the back of each rat with Hollister® medical adhesive. The inside edge of the appliance was about 0.5 cm outside the dose area. Total treated skin area for each animal was approximately 29 cm^2.

C. Administration of the Doses

Doses were applied to the premarked skin areas using an 18 gauge gavage needle (balled-tipped) attached to a 500 µL glass syringe equipped with a Teflon®-tipped plunger (Hamilton #1725). The dose solution was spread evenly over the area with the side of the needle. After the application, a rectangular piece of 50/50 polyester/cotton sheeting was affixed on top of the protective frame. The animals were, thereafter, housed individually in glass metabolism chambers suitable for the separate collection of urine and feces.

D. Sample Collection and Analysis

The sacrifice times for each dose group were 1, 4, 10, 24, 48, 72, and 96 hours after dose application. The first four sacrifice times of 1, 4, 10, and 24 hours received 1, 4, 10, and 24 hours of exposure, respectively. For the 48, 72, and 96 hour sacrifice times, the animals were exposed to Devrinol® and the treated skin sites were washed by gentle scrubbing with gauze soaked in soapy water at the end of 24 hours; these animals were, thereafter, returned to the metabolic chambers. At the termination of the study, animals were anesthetized with ketamine:xylazine (7:1). Animals were killed by injection of about 0.2 mL of T-61 euthanasia solution directly into the heart. Blood and urine samples were collected for analysis. The treated skin site was excised and then washed with soapy water (ca. 30 mL of Liquid Ivory®/liter), scrubbed with swabs of cotton gauze, rinsed with water and again scrubbed with swabs of cotton gauze. A total of about 80 mL of liquid, both soapy water and water rinse, was used to wash the skin. Samples collected for analysis were: protective appliance, skin wash, treated skin site, blood, carcass, feces, and urine (including cage washes).

E. Determination of the Results

Recoveries of administered doses shown in Table 1 are grouped into percent dose absorbed, unabsorbed dose and total dose recovery. The majority of the dose for all dose groups was unabsorbed ranging from 69 to 98 percent depending on exposure and sacrifice times. Percent doses in treated skin sites for all dose groups were generally low. These skin residues are considered absorbed. Percent dose absorbed as shown in Table 1 was the sum of percent dose in treated skin area, carcass, urine and feces. These dermal absorption values are adjusted for total dose recovery. Percent dose absorbed is generally greater for the longer exposure and sacrifice times for the same dose level. The results of the study also indicated that percent dermal absorption of Devrinol® is generally dose dependent, i.e., the percent dose absorbed decreased with increasing dose levels. For example, a dermal absorption value of 27.4% was obtained for the dose D (45 µg/cm^2); whereas, lower dermal absorption values were observed for doses A (2%), B (17.1%) and C (16.4%) after animals were exposed for 24 hours and sacrificed 96 hours post dose. Percent of dose in blood was insignificant.

Bioavailability of bound skin residues was determined by using an asymptotic plot (Thongsinthusak *et al*., 1993). An exponential saturation model with lag time employed for this purpose is represented by $Y = A[1-e^{-B(X+C)}]$ or Recov = MAX*(1-EXP(-RATE*(TIME + LAG))) (Thongsinthusak and Ross, 1994). Whenever bioavailability of bound skin residues can be determined, residues remain at the treated skin sites will be disregarded in the calculation of a dermal absorption value. Cumulative excretion of doses for the 24, 48, 72, and 96 hour sacrifice times (Table 2) were used in this extrapolation. Maximum excretion for three high dose groups could not be determined because iterations did not converge asymptotically. Maximum excretion

of the lowest dose group was determined to be 28.1%. An example of the plot is shown in Figure 1. The dermal absorption value for the 45 $\mu g/cm^2$ dose group was estimated to be 30.3% (Table 3). The results from this extrapolation were not used in the final determination of dermal absorption values because bound skin residues in all dose groups and sacrifice times are low; these residues were already included in the calculation of dermal absorption in Table 1.

The lowest dose of 45 $\mu g/cm^2$ used in this study is considered too high when compared to a general exposure range experienced by agricultural workers. We routinely recommend a lower dose, e.g., 1-6 $\mu g/cm^2$ for the lowest dose group. From the results shown in Tables 1, dermal absorption values increased approximately two-fold for all exposure and sacrifice times when the dose was reduced from 88 to 45 $\mu g/cm^2$. Similar results were also observed when the exposure time was extended from 10 hours to 24 hours. To compensate for the higher dose used, we have used dermal absorption values from the 24-hour exposure time for the 45 $\mu g/cm^2$ (lowest) dose group. Therefore, a mean dermal absorption value from 24, 48, 72, and 96-hour sacrifice times of 24.7% is appropriate to be used in the exposure estimates. Other dermal absorption values from higher dose levels may be applied if human exposures obtained from field studies are similar to these dose levels.

Recommendations:

1. The dermal absorption study of napropamide (Devrinol®) in male rats, as reported in pesticide registration document number 328-095, is acceptable.

2. A dermal absorption value of 24.7 percent or other values depending on exposure levels may be used to estimate absorbed dosages of persons exposed to Devrinol®, unless human dermal absorption data are available.

References:

Thongsinthusak, T., Ross, J. H., and Meinders, D. 1993. Guidance for the Preparation of Human Pesticide Exposure Assessment Documents. HS-1612. Worker Health and Safety Branch, California Department of Pesticide Regulation. pp. 4-5.

Thongsinthusak, T., and Ross, J. 1994. Determination of dermal absorption of pesticides in animals. A memorandum to John Donahue dated April 7, 1994. Worker Health and Safety Branch, California Department of Pesticide Regulation.

cc: Joshua Johnson (1 original, 5 copies)
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(TCW/dermal/Devrin1)

Table 1. Recovery of administered dose of napropamide.

		Percent dose (mean)					
Dose (a.i.)	Sacrifice time (h)	Unabsorbed dose *a	Treated skin site	Carcass	Urine	Feces	Total recovery
Dose A *b	1	95.4	1.7	0.06	0	0	97.2
2686 µg/cm²			(1-h) % Dose absorbed*c =	1.8			
	4	81.1	0.82	0.04	0	0	82.0
			(4-h) % Dose absorbed*c =	1.0			
	10	92.1	1.37	0.14	0.01	0	93.6
			(10-h) % Dose absorbed*c =	1.6			
	24	92.5	0.42	0.14	0.04	0.02	93.1
			(24-h) % Dose absorbed*c =	0.7			
	48	87.8	0.66	0.38	0.27	0.21	89.3
			(48-h) % Dose absorbed*c =	1.7			
	72	92.7	0.31	0.41	0.51	0.42	94.4
			(72-h) % Dose absorbed*c =	1.7			
	96	85.6	0.31	0.24	0.69	0.5	87.3
			(96-h) % Dose absorbed*c =	2.0			
Dose B *b	1	91.5	2.68	0.19	0.01	0	94.4
192 µg/cm²			(1-h) % Dose absorbed*c =	3.1			
	4	90.7	3.1	0.65	0.07	0	94.5
			(4-h) % Dose absorbed*c =	4.0			
	10	90.4	3.01	1.43	0.36	0.03	95.2
			(10-h) % Dose absorbed*c =	5.1			
	24	84.3	1.14	2.76	1.96	1.11	91.3
			(24-h) % Dose absorbed*c =	7.6			
	48	83.2	1.12	1.93	2.87	2.41	91.5
			(48-h) % Dose absorbed*c =	9.1			
	72	80.1	0.84	1.06	4.58	4.24	90.8
			(72-h) % Dose absorbed*c =	11.8			
	96	72.0	0.75	1.59	5.92	6.61	86.9
			(96-h) % Dose absorbed*c =	17.1			
Dose C *b	1	97.9	1.76	0.21	0.01	0	99.9
88 µg/cm²			(1-h) % Dose absorbed*c =	2.0			
	4	98.0	1.29	1.05	0.12	0	100.5
			(4-h) % Dose absorbed*c =	2.4			
	10	93.8	2.75	3.26	0.67	0.1	100.6
			(10-h) % Dose absorbed*c =	6.78			
	24	80.3	1.01	5.64	3.6	1.4	91.9
			(24-h) % Dose absorbed*c =	12.7			
	48	80.2	0.58	1.8	5.13	4.45	92.2
			(48-h) % Dose absorbed*c =	13.0			
	72	76.6	0.38	0.76	7.25	6.87	91.9
			(72-h) % Dose absorbed*c =	16.6			
	96	76.7	0.45	0.37	7.81	6.45	91.8
			(96-h) % Dose absorbed*c =	16.4			

		Percent dose (mean)					
Dose (a.i.)	Sacrifice time (h)	Unabsorbed dose *a	Treated skin site	Carcass	Urine	Feces	Total recovery
Dose D *b	1	98.6	2.64	0.44	0.02	0	101.7
45 µg/cm²			(1-h) % Dose absorbed*c =		3.0		
	4	94.9	3.13	1.76	0.22	0	100.0
			(4-h) % Dose absorbed*c =		5.1		
	10	88.7	3.56	5.52	1.5	0.01	99.3
			(10-h) % Dose absorbed*c =		10.7		
	24	72.7	1.79	9.78	6.52	2.36	93.2
			(24-h) % Dose absorbed*c =		22.0		
	48	73.2	0.92	3.4	10.5	6.83	94.9
			(48-h) % Dose absorbed*c =		22.8		
	72	72.0	0.92	0.92	14.74	9.18	97.8
			(72-h) % Dose absorbed*c =		26.4		
	96	69.0	0.54	0.71	12.56	12.27	95.1
			(96-h) % Dose absorbed*c =		27.4		

*a Percent dose recovered from protective appliance and skin washes.
*b A treated skin site was 29 cm².
*c When bioavailability of bound skin residues cannot be determined, dermal absorption value = (% Dose recovered from the treated skin site + carcass + urine + feces) x 100/Total recovery (%).

Table 2. Percent dose of napropamide (Devrinol) excreted following 24-hour exposure.

Dose A — Cumulative % dose (mean)

2686 µg/cm²

Time (h)	Urine (U)	Feces (F)	U + F
24	0.04	0.02	0.06
48	0.27	0.21	0.48
72	0.51	0.42	0.93
96	0.69	0.5	1.19

Dose B — Cumulative % dose (mean)

192 µg/cm²

Time (h)	Urine (U)	Feces (F)	U + F
24	1.96	1.11	3.07
48	2.87	2.41	5.28
72	4.58	4.24	8.82
96	5.92	6.61	12.53

Dose C — Cumulative % dose (mean)

88 µg/cm²

Time (h)	Urine (U)	Feces (F)	U + F
24	3.59	1.4	4.99
48	5.13	4.45	9.58
72	7.25	6.87	14.12
96	7.81	6.45	14.26

Dose D — Cumulative % dose (mean)

45 µg/cm²

Time (h)	Urine (U)	Feces (F)	U + F
24	6.52	2.36	8.88
48	10.5	6.83	17.33
72	14.74	9.18	23.92
96	12.56	12.27	24.83

Table 3. Dermal absorption of napropamide in male rats determined from asymptotic plots*a.

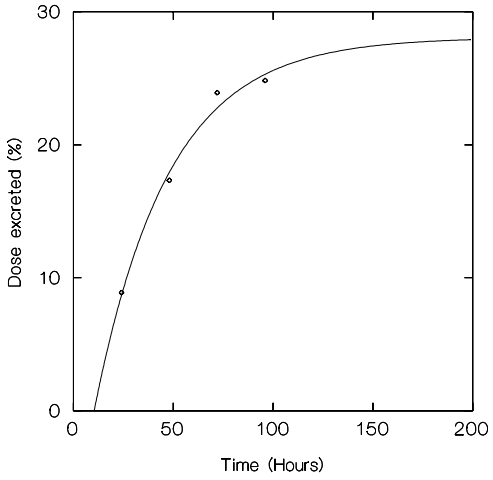
Dose	Percent dose (mean)*b				
(µg/cm²)	Excreted*c	Carcass	Sub-total	Recovery(%)	Total abs.*d
2686	N/A	0.24	N/A	87.3	N/A
192	N/A	1.59	N/A	86.9	N/A
88	N/A	0.37	N/A	91.8	N/A
45	28.1	0.71	28.81	95.1	30.3

*a Based on 24-hour exposure time and the longest sacrifice time of 96 hours.
*b Percent dose: maximum excretion + carcass.
c At asymptote using an exponential saturation model (Y = Max(1-EXP(-RATE*(X - LAG))).
*d Adjusted to reflect 100% recovery.
N/A - Maximum excretion could not be determined from a plot using an exponential saturation model.

(TXL/Dermal/Devrin1)

Figure 1. Asymptotic plot of percent dose excreted in urine and feces after topical administration of napropamide (Devrinol®) at 45 ug/cm^2 (or 1.31 mg/animal)

$$Y = 28.075*(1-EXP(-0.027*(X-10.316)))$$



Statistics:

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ITERATION	LOSS	PARAMETER VALUES		
0	.1553116D+04	.1000D+00	.1000D+00	.1000D+00
1	.1631282D+03	.1874D+02	.7888D+00	.1024D+00
2	.1631282D+03	.1874D+02	.7889D+00	.1024D+00
3	.1631282D+03	.1874D+02	.7887D+00	.1023D+00
4	.1624943D+03	.1874D+02	.2665D+00	-.1072D+00
5	.1314384D+03	.1875D+02	.9961D-01	-.1718D+00
6	.9124065D+02	.1875D+02	.5424D-01	-.1893D+00
7	.8904370D+02	.1875D+02	.4060D-01	-.1945D+00
8	.4355481D+02	.2163D+02	.4376D-01	-.2684D+01
9	.1004835D+02	.2522D+02	.2867D-01	-.7259D+01
10	.3671570D+01	.2729D+02	.3329D-01	-.1207D+02
11	.2105922D+01	.2728D+02	.3052D-01	-.1187D+02
12	.2068508D+01	.2716D+02	.3036D-01	-.1142D+02
13	.2021719D+01	.2742D+02	.2965D-01	-.1142D+02
14	.1946929D+01	.2790D+02	.2796D-01	-.1082D+02
15	.1928030D+01	.2801D+02	.2755D-01	-.1050D+02
16	.1926282D+01	.2809D+02	.2714D-01	-.1028D+02
17	.1925563D+01	.2807D+02	.2726D-01	-.1032D+02
18	.1925560D+01	.2807D+02	.2725D-01	-.1032D+02
19	.1925560D+01	.2808D+02	.2725D-01	-.1032D+02
20	.1925560D+01	.2808D+02	.2725D-01	-.1032D+02

(TCW/Dermal/Devrin2

DEPENDENT VARIABLE IS RECOV

SOURCE	SUM-OF-SQUARES	DF	MEAN-SQUARE
REGRESSION	1565.953	3	521.984
RESIDUAL	1.926	1	1.926
TOTAL	1567.879	4	
CORRECTED	163.128	3	

RAW R-SQUARED (1-RESIDUAL/TOTAL) = 0.999
CORRECTED R-SQUARED (1-RESIDUAL/CORRECTED) = 0.988

PARAMETER	ESTIMATE	A.S.E.	LOWER <95%>	UPPER
MAX	28.075	3.439	-15.621	71.772
RATE	0.027	0.011	-0.110	0.165
LAG	-10.316	5.172	-76.039	55.406

ASYMPTOTIC CORRELATION MATRIX OF PARAMETERS

	MAX	RATE	LAG
MAX	1.000		
RATE	-0.933	1.000	
LAG	0.663	-0.837	1.000

Kathy Wynn, Registration Specialist
Pesticide Registration Branch

January 3, 1995

Sacramento

445-4267

-Tom Thongsinthusak, Staff Toxicologist
Worker Health and Safety Branch

PRODUCT NAME: Permethrin
ACTIVE INGREDIENT: Permethrin
COMPANY NAME: Zeneca
I.D. NUMBER: SBC-142489-E
DOCUMENT NUMBER: 378-483
EPA REGISTRATION NUMBER: 10182-0-
TITLE: Permethrin: *In Vivo* Percutaneous Absorption in the Rat

A dermal absorption study of [^{14}C]-labeled permethrin emulsion concentrate and three aqueous dilutions of this formulation in male rats was conducted by Zeneca Central Toxicology Laboratory in the United Kingdom. This study was conducted in compliance with U.S. Good Laboratory Practice standards and other standards set by the United Kingdom and Japan. Various phases of the study were inspected by the quality assurance (QA) officer and the head of the QA unit signed the final report. A summary of this dermal absorption study and the evaluation of the results are presented below.

A. Test substances

Both labeled and unlabeled permethrin were used in the study. Unlabeled permethrin had a cis/trans isomeric ratio of 44.6:55.4. It had a purity of 99.4% w/w. [^{14}C]-Cyclopropyl-labeled permethrin had a cis/trans isomeric ratio of 44.6:55.4 and a radiochemical purity of >99%. For the preparation of the dose, labeled and unlabeled test substances were mixed in a blank formulation concentrate to give permethrin 2EC (2 lb a.i./gal (U.S.)). The highest administered dose used was undiluted concentrate. Aqueous dilutions of the formulation concentrate in deionized water were prepared for three lower doses. The four dose levels used in the study were 0.004, 0.08, 0.86, and 9.1 mg/animal equivalent to 0.4, 8, 86, and 910 μg/cm^2, respectively.

B. Preparation of Animals

Approximately 5-9 week old adult male Alderly Park Wistar strain rats (Alpk:APfSD) were used in the study. Body weights of these rats ranged from 180 to 255 gm. These animals were inspected and acclimatized for at least three days prior to dosing. The temperature in the animal room ranged from 19 to 23 ^{o}C and the relative humidity from 40 to 70%. The photo period was 12 hour light and dark cycles. Approximately 24 hours prior to the dosing, the fur from the shoulders and back of each rat was shaved. The shaved area of skin was washed with acetone to remove sebum. Two 2.5 mm internal diameter, 3 mm thick nitrile rubber "O" rings were glued to the shaved skin surface, one behind each shoulder, using cyano-acrylate glue. The internal surface area of skin encompassed by each ring was approximately 5 cm^2. Total treated skin area for each animal was approximately 10 cm^2 . A Queen Anne plastic collar was secured around the neck of each animal; these animals were then transferred to individual stainless steel metabolism cages and were allowed to acclimatize overnight. Four animals were used per sacrifice time for each dose.

C. Administration of the Doses

The dose preparation of 20 µL was applied by using a 25 µL capacity positive displacement pipette to the skin surface within one "O" ring and was spread over 5 cm^2. The treated skin sites were allowed to dry. A protective cover made of a fine permeable nylon gauze (100 µm bolting cloth) was glued to the surface of the ring with Bostik. For the 0.86 mg/animal dose the nylon gauze was replaced with an activated carbon filter pad. The same dosing procedure was then repeated for the second application site of the same animal. The animals were thereafter placed in individual stainless steel metabolism cages, suitable for the separate collection of urine and feces.

D. Sample Collection and Analysis

The exposure (and sacrifice) times for all dose groups of animals were: 0.5, 1, 2, 4, 10, and 24 hours. Before sacrifice, animals were anesthetized with Fluothane vapor. After the protective cover was removed, the treated skin site was washed by swabbing with a 3% aqueous solution of Teepol-L using natural sponge swabs. The treated skin surface was then rinsed by swabbing with water using natural sponge swabs. Samples collected for analysis were: nonocclusive covers, skin wash swabs, tape stripped stratum corneum, treated and untreated skin samples, cage washings, blood, carcasses, feces, and urine.

E. Determination of the Results

Recovery of administered doses of permethrin for the 0.5, 1, 2, 4, 10, and 24-hour sacrifice times are shown in Table 1. Percent unabsorbed dose was the sum of percent dose recovered in skin washes, protective cover, and untreated skin. The administered dose recovered in the treated skin sites (stratum corneum and residual application site) are considered absorbed. The Department, upon review of a dermal absorption study protocol, routinely recommends an additional group of animals for each dose group at a longer sacrifice time. This will allow daily collection of excreta for an extended observation period, e.g., 4-7 days. Percent dose recovered in excreta (urine and feces) samples will be used to determine bioavailability of bound skin residues by using an asymptotic plot (Thongsinthusak *et al*., 1993). An exponential saturation model with lag time employed for this purpose is represented by $Y = A[1-e^{-B(X+C)}]$ or Recov = MAX*(1-EXP(-RATE*(TIME+LAG))) (Thongsinthusak and Ross, 1994). Whenever bioavailability of bound skin residues can be determined, residues remain at the treated skin sites will be disregarded in the calculation of a dermal absorption value. We assume that residues in the stratum corneum and the application site are bioavailable for further absorption and systemic circulation during the exposure period of the study and thereafter, unless more definitive data are available. This is in contrast to what was mentioned in the submitted report (Doc. No. 378-483, page 31, paragraph 2). Therefore, we calculated percent dose absorbed as the sum of percent dose recovered in treated skin site, stratum corneum, blood, carcass, urine, feces and cage wash.

The results of the study indicated that percent dermal absorption of permethrin is generally dose dependent. For example, percent dose absorbed for the low doses (0.4 and 8 µg/cm^2) is higher than that for the higher doses (86 and 910 µg/cm^2). Also, percent dose absorbed is generally greater for the longer exposure and sacrifice times for the same dose level. Percent of dose in blood was estimated and shown in Table 2. It can be seen that percent of dose in blood is very low ranging from 0.19 to 0.34% for the lowest dose group.

Table 3 summarizes the dermal absorption values for all dose groups and sacrifice times. It is rather odd for the dose level 8 $\mu g/cm^2$ to give higher dermal absorption values than the lower dose; the pattern of absorption for the other three dose levels indicates lower absorption for higher dose levels. The average adjusted dermal absorption values for the two low doses (0.4 and 8 $\mu g/cm^2$) with 10-hour exposure time is 28%. This dermal absorption value is appropriate to be used in the exposure estimates because this dose should be representative of an exposure range experienced by agricultural workers. Other dermal absorption values may be applied if human exposures obtained from field studies fall outside this range.

Recommendations:

1. The dermal absorption study of permethrin in male rats, as reported in pesticide registration document number 378-483, is acceptable.

2. A dermal absorption value of 28 percent or other values depending on exposure levels may be used to estimate absorbed dosages of persons exposed to permethrin, unless human dermal absorption data are available.

References:

Thongsinthusak, T., Ross, J. H., and Meinders, D. 1993. Guidance for the Preparation of Human Pesticide Exposure Assessment Documents. HS-1612. Worker Health and Safely Branch, California Department of Pesticide Regulation. pp. 4-5.

Thongsinthusak, T., and Ross, J. 1994. Determination of dermal absorption of pesticides in animals. A memorandum to John Donahue dated April 7, 1994. Worker Health and Safety Branch, California Department of Pesticide Regulation.

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(TCW/dermal/Permeth1)

Table 1. Recovery of administered dose of permethrin.

	Percent dose (mean)								
Dose (a.i.)	Sacrifice time (hour)	Unab-sorbed*a	Treated skin site*b	Blood	Urine	Feces	Carcass	Cage wash	Total recovery
(A) 0.004 mg/animal (0.4 µg/cm²)*d	0.5	79.84	19.19	0.19	0.02	0.01	2.37	0.10	101.72
			*(0.5-h) Absorbed dose (% dose)*c =*		*21.88*				
	1	79.54	18.2	0.19	0.02	0.01	1.97	0.10	100.03
			*(1-h) Absorbed dose (% dose)*c =*		*20.49*				
	2	79.29	16.44	*0.19*	0.02	0.01	1.92	0.10	97.97
			*(2-h) Absorbed dose (% dose)*c =*		*18.68*				
	4	71.9	25.09	0.19	0.08	0.02	2.06	0.10	99.44
			*(4-h) Absorbed dose (% dose)*c =*		*27.54*				
	10	72.86	17.67	0.19	0.54	0.01	3.47	0.15	94.89
			*(10-h) Absorbed dose (% dose)*c=*		*22.03*				
	24	66.24	18.29	0.34	2.45	1.17	7.08	0.42	95.99
			*(24-h) Absorbed dose (% dose)*c=*		*29.75*				
(B) 0.08 mg/animal (8 µg/cm²)*d	0.5	61.78	35.27	0.02	0.01	0.01	0.24	0.01	97.34
			*(0.5-h) Absorbed dose (% dose)*c =*		*35.56*				
	1	65.79	33.59	0.02	0.01	0	0.48	0.02	99.91
			*(1-h) Absorbed dose (% dose)*c =*		*34.12*				
	2	67.87	38.05	0.02	0.01	0.01	0.64	0.02	106.62
			*(2-h) Absorbed dose (% dose)*c =*		*38.75*				
	4	66.68	31.86	0.06	0.04	0.01	1.23	0.02	99.90
			*(4-h) Absorbed dose (% dose)*c =*		*33.22*				
	10	65.61	28.36	0.09	0.32	0.01	3.20	0.04	97.63
			*(10-h) Absorbed dose (% dose)*c=*		*32.02*				
	24	53.28	34.2	0.13	2.72	0.81	6.29	0.24	97.67
			*(24-h) Absorbed dose (% dose)*c=*		*44.39*				

Table 1. (cont.) Percent recovery of administered dose of permethrin.

	Percent dose (mean)								
Dose (a.i.)	Sacrifice time (hour)	Unab-sorbed*a	Treated skin site*b	Blood	Urine	Feces	Carcass	Cage wash	Total recovery
(C) 0.86 mg/animal	0.5	84.74	11.62	0.02	0.01	0.01	0.56	0.01	96.97
(86 µg/cm²)*d			*(0.5-h) Absorbed dose (% dose)*c=*		*12.23*				
	1	85.2	12.54	0.03	0.01	0.01	0.40	0.01	98.20
			*(1-h) Absorbed dose (% dose)*c =*		*13*				
	2	85.47	12.77	0.04	0.01	0.01	0.31	0.01	98.62
			*(2-h) Absorbed dose (% dose)*c =*		*13.15*				
	4	78.65	17.17	0.07	0.02	0.01	0.87	0.02	96.81
			*(4-h) Absorbed dose (% dose)*c =*		*18.16*				
	10	79.4	15.42	0.05	0.2	0.01	2.21	0.03	97.32
			*(10-h) Absorbed dose (% dose)*c=*		*17.92*				
	24	72.34	13.38	0.03	2.04	0.87	5.49	0.21	94.36
			*(24-h) Absorbed dose (% dose)*c=*		*22.02*				
(D) 9.1 mg/animal	0.5	95.45	2.49	0.01	0.01	0.01	0.15	0.01	98.13
(910 µg/cm²)*d			*(0.5-h) Absorbed dose (% dose)*c=*		*2.68*				
	1	94.86	2.19	0.01	0.01	0.01	0.18	0.01	97.27
			*(1-h) Absorbed dose (% dose)*c =*		*2.41*				
	2	93.1	3.47	0.01	0.01	0	0.59	0.01	97.19
			*(2-h) Absorbed dose (% dose)*c =*		*4.09*				
	4	90.93	2.97	0.02	0.01	0.01	1.16	0.02	95.12
			*(4-h) Absorbed dose (% dose)*c =*		*4.19*				
	10	90.83	2.8	0.03	0.09	0.01	1.14	0.02	94.92
			*(10-h) Absorbed dose (% dose)*c=*		*4.09*				
	24	83.92	5.05	0.06	0.81	0.14	2.64	0.12	92.74
			*(24-h) Absorbed dose (% dose)*c=*		*8.82*				

*a Skin wash + protective cover + untreated skin (TXL/Dermal/Permeth1)

*b Residues from application site + stratum corneum

*c When bioavailability of bound skin residues cannot be determined by an asymptotic plot, a demal absorption value = % dose recovered from the treated skin site + blood + urine + feces + carcass + cage wash

*d Treated skin site = 10 cm²

Table 2. Percent dose of permethrin in blood.

Permethrin in whole blood

Sacrifice time	0.4 ug/cm2			8 ug/cm2			86 ug/cm2			910 ug/cm2		
(hour)	ug equiv./g	ug/animal	% dose	ug equiv./g	ug/animal	% dose	ug equiv./g	ug/animal	% dose	ug equiv./g	ug/animal	% dose
0.5	0.0005	0.0075	0.19	0.001	0.015	0.02	0.011	0.165	0.02	0.069	1.035	0.01
1	0.0005	0.0075	0.19	0.001	0.015	0.02	0.019	0.285	0.03	0.075	1.125	0.01
2	0.0005	0.0075	0.19	0.001	0.015	0.02	0.022	0.330	0.04	0.084	1.260	0.01
4	0.0005	0.0075	0.19	0.003	0.045	0.06	0.041	0.615	0.07	0.135	2.025	0.02
10	0.0005	0.0075	0.19	0.005	0.075	0.09	0.029	0.435	0.05	0.201	3.015	0.03
24	0.0009	0.0135	0.34	0.007	0.105	0.13	0.015	0.225	0.03	0.382	5.730	0.06

Notes:

1. Assumed 15 grams of whole blood/animal.
2. Values were calculated from data reported in Pesticide Registration Document Number 378-483.

Table 3. Adjusted percent dermal absorption of permethrin in male rats.

Dermal absorption of permethrin (%)

Sacrifice time	0.4 ug/cm2			8 ug/cm2			86 ug/cm2			910 ug/cm2		
(hour)	Dose abs.	Recovery	Adj. dose	Dose abs.	Recovery	Adj. dose	Dose abs.	Recovery	Adj. dose	Dose abs.	Recovery	Adj. dose
0.5	21.9	101.7	21.53	35.6	97.3	36.59	12.2	97.0	12.58	2.7	98.1	2.75
1	20.5	100.0	20.50	34.1	99.9	34.13	13.0	98.2	13.24	2.4	97.3	2.47
2	18.7	98.0	19.08	38.8	106.6	36.40	13.2	98.6	13.39	4.1	97.2	4.22
4	27.5	99.4	27.67	33.2	99.9	33.23	18.2	96.8	18.80	4.2	95.1	4.42
10	22.0	94.9	23.18	32.0	97.6	32.79	17.9	97.3	18.40	4.1	94.9	4.32
24	29.8	96.0	31.04	44.4	97.7	45.45	22.0	94.4	23.31	8.8	92.7	9.49

Dose abs. = % Dose absorbed; Recovery = Total dose recovered (%); Adj. dose = % Dermal absorption (or % Dose abs. x 100/% Recovery)

(TXL\Dermal\Permeth2)

Sate of California

Memorandum

To : Phil Anderson, Registration Specialist
Pesticide Registration Branch
Place : Sacramento
Via : John Ross, Senior Toxicologist
Worker Health and Safety Branch

Date : July 26, 1990

Phone : 5-8474

From : **Department of Food and Agriculture** - Tian Thongsinthusak, Staff Toxicologist
Worker Health and Safety Branch

Subject : PRODUCT NAME: DDVP technical
ACTIVE INGREDIENT: dichlorvos
COMPANY NAME: Amvac Chemical Corporation
I.D. NUMBER: SBC-122288-E
DOCUMENT NUMBER: 235-101
EPA REGISTRATION NUMBER: 5481-96
TITLE: Dermal absorption of dichlorvos in rats (1990)

The report of the dermal absorption study of dichlorvos (DDVP) technical in male rats has been submitted by the registrant, Amvac Chemical Corporation. The protocol for this study was previously reviewed and critiqued by the Worker Health and Safety Branch (Tian Thongsinthusak, memorandum, October 5, 1989). This study was performed by the Research Triangle Institute (RTI), North Carolina. According to the final report some deviations were made from the protocol; however, such modifications were not expected to constitute any significant changes in the outcome of the results.

Male rats ((Crl:CDR(SD)BR) used in this study were purchased from Charles River Laboratory. The average rat weight for all dose groups was 226-240 g. All rats were inspected, acclimatized, and identified accordingly at the study site before the study. Approximately 24 hours before dosing, the rats were sedated (60 mg/kg of ketamine:xylazine, 7:1) and the fur on the back was removed with a No. 40 animal clipper (Oster Professional Product). The clipped area was wiped with a gauze soaked in acetone and dried. The treatment area was demarcated using a permanent type felt tip marker.

A non-occlusive protective appliance was used to prevent loss of chemical from the treated site. The appliance consisted of a frame with a window covered with a piece of charcoal-impregnated filter (3M Company, Cat. No. 9913). The frame was made of 6x7xl cm (length x width x thickness) Reston^{R} self-adhering foam pad (3M^{TM}). A 4x5 cm window was cut in the center pad. The protective appliance was attached to rat skin before dosing by using double sided carpet tape (Cat. No. DFC-1, Manco, Inc., Cleveland, OH). Radiolabeled DDVP, ((1-^{14}C)-2,2-dichlorovinyl)dimethyl phosphate with radio purity greater than 95 percent, was used in the study. Unlabeled DDVP was

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also used to mix with ^{14}C-DDVP for the highest dose. The purity of ^{14}C-DDVP was also analyzed after dosing and it averaged 93 percent (92.9, 92.8 and 93.5 percent).

Three dose levels used in the study were 360, 36, and 3.6 ug/rat equivalent to 30, 3, and 0. 3 ug/cm^2 respectively for rat group A, B, and C. Each dose group was subdivided into 3 sacrifice times of 10, 24, and 120 hours. Four male rats (not including spare rats in each dose group) were used for each sacrifice time.

DDVP dosing solution was prepared in water and 100 uL of dosing solution containing different dose levels was administered to 12 cm^2 of clipped back of each rat. The administered dose was delivered to the treatment area by using an 18 gauge gavage needle (ball-tipped) attached to a 500 uL glass syringe equipped with a Teflon plunger (Hamilton No. 1750). During the administration of the dose, volatile DDVP was trapped by a sorbent charcoal tube attached to the small end of a funnel that was positioned near the dosed site. Air near the application site was drawn through the funnel at a rate of approximately 10 liters/min. One tube was used per rat. After dosing, the protective appliance was covered with charcoal- impregnated filter and 50/50 polyester/cotton sheeting. A curved tent of aluminum grille was then secured over the protective appliance in such a manner that only the outside edge of the grille was in contact with the appliance. Treated rats were housed individually in glass metabolic chambers.

Exhaled $^{14}C0_2$ from each rat was trapped by pulling air from the chamber through a series of two traps each containing 400-600 mL of 1 N sodium hydroxide. Urine and feces were collected separately in round bottom flasks. Collection periods were at 10 hours, 24 hours and each subsequent 24 hour period until the rats were sacrificed.

At the end of a 10-hour exposure, the protective appliance was removed and the treatment site was gently scrubbed with gauze soaked in soapy water (3% liquid Ivory in water, v/v) and 4 rats from each dose group were sacrificed. Fresh and complete protective appliances were affixed to treatment sites of rats with sacrifice times of 24 and 120 hours. Therefore, all rats were returned to the metabolic chambers. Groups of 4 rats were sacrificed at the end of 24 and 120 hours for the 3 and 0.3 ug/cm^2 dose groups. The 30 ug/cm^2 rats were sacrificed at the end of 24 and 102 hours (instead of 120 hours due to an impending ice storm at the study site).

Recovered radioactivity in each sample was reported in term of percent administered dose (AD) and the results were reported in Table 1-3 (attached). Table 1 shows the results without any corrections of the percent recovered AD. The overall total recovery ranged from 85.8-93.1%. According to the final report the performing laboratory has made corrections for percent AD recovered in charcoal filter #1 (but not charcoal filter #2) for all dose groups (Table 2). The percent spiked recoveries for charcoal filter used in the corrections were 92.5, 89.8 and 88.6 percent for group A,

B. and C, respectively. The total recovery (corrected) shown in Table 2 reflected the results of corrections made for charcoal filter No.1 by RTI and corrections to all other samples by the reviewer using the percent recovery reported in Table 1. As a result, the total recovery of the administered dose after appropriate corrections ranged from 96.0 to 99. 3 percent. The percent administered dose absorbed, unabsorbed and in dosed skin are summarized in Table 3.

Bioavailability of bound skin residues which ranged from 13.6 to 22.5 percent was determined by performing semi - logarithmic plots of collection time in hours versus the sum of percent AD recovered in exhaled $C0_2$, urine and feces (Fig. 1). Curves of the high dose, 30 ug/cm^2 plateaud at approximately 100 hours after the exposure. Whereas, for the 3 ug/cm^2 and 0.3 ug/cm^2 doses, a plateau had not been reached at the end of 120 hours, but the percent AD in $C0_2$, urine and feces increased slowly 48 hours after dosing. The results from this study showed that the highest dose (30 ug/cm^2) gave the highest percent dermal absorption. The curves of the lower doses are expected to behave similarly to the highest dose if the dose levels of the two lower doses are increased. It is assumed from this interpretation that the bound skin residues will not result in substantial bioavailability for further absorption and thus the observation period of 120 hours is deemed adequate.

The summary of the percent dermal absorption for all dose levels of DDVP technical is shown in Table 4. For the prolonged observation period of up to 120 hours the percent dermal absorption ranges from 10 to 13 %. Dermal absorption for the shorter observation periods of 10 and 24 hours was not considered due to the continued elimination of AD in urine, feces and exhaled $C0_2$ Dermal absorption of DDVP technical in male rats was determined to be 13 percent.

Recommendations:

1. Dermal absorption of 13 percent for DDVP technical is appropriate to be used in the human exposure estimates. The dose levels used in the study are expected to cover the ranges of actual worker exposure.

2. This study is acceptable.

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Dermal absorption of DDVP technical in male rats after 10 hour exposure

Table 1. Percent recovery of administered dose (corrections were not made for all columns).

		Mean % administered dose (AD)														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Dose	Sacrifice time(h)	Carcass	Blood Aliquot	Exhaled CO_2	Urine	Feces	Cage rinses	Dosed skin	Dose site Wash #1	Dose site Wash #2	Appliance # 1	Appliance # 2	Charcoal filter # 1	Charcoal filter # 2	Dosing trap	Total recovery (uncorrected)
Group A	10.0	6.3	0.2	3.1	1.2	0.1	0.6	19.3	12.6	0.0	7.5	0.0	35.0	a	a	85.8
(30 ug/cm^2)	24.0	4.8	0.1	3.5	1.5	0.2	0.1	15.4	11.0	1.7	6.8	0.4	43.3	a	a	88.7
	102.0 b	3.9	0.1	4.9	2.0	0.5	0.1	12.1	12.4	1.1	7.5	0.4	43.8	a	a	88.8
Group B	10.0	5.1	0.2	2.7	1.3	0.1	0.2	20.0	11.3	0.0	9.1	0.0	39.4	0.0	0.1	89.5
(3 ug/cm^2)	24.0	4.1	0.2	3.3	1.6	0.3	0.1	13.6	11.3	1.2	8.8	0.3	41.5	0.2	0.1	86.5
	120.0	3.3	0.1	4.6	2.2	1.0	0.0	16.3	9.7	1.0	9.3	0.6	39.0	1.0	0.1	87.8
Group C	10.0	2.9	0.2	2.2	1.0	0.1	0.2	18.2	10.3	0.0	5.6	0.0	48.6	0.0	0.1	89.3
(0.3 ug/cm^2)	24.0	4.0	0.2	3.5	1.5	0.3	0.2	12.4	11.1	1.7	11.8	0.4	41.9	0.5	0.0	89.6
	120.0	1.5	0.1	3.9	1.8	1.6	0.1	17.1	7.8	1.1	7.9	0.6	48.4	1.2	0.1	93.1

a Because of the low concentration in dose group B and C these samples were not analyzed.
b Shortened from 120 hours due to impending ice storm at the study site.
Col. 12 (charcoal filter #1). Corrections were not made for percent recovery of fortified samples.

Table 2. Percent recovery of administered dose (corrections were made based on % total recovery listed in Table 1).

		Mean % adminisered dose (AD)														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Dose	Sacrifice time(h)	Carcass	Blood Aliquot	Exhaled CO_2	Urine	Feces	Cage rinses	Dosed skin	Dose site Wash #1	Dose site Wash #2	Appliance # 1	Appliance # 2	Charcoal filter # 1	Charcoal filter # 2	Dosing trap	Total recovery (uncorrected)
Group A	10.0	7.3	0.2	3.6	1.4	0.1	0.7	22.5	14.7	0.0	8.8	0.0	37.7	a	a	96.9
(30 ug/cm2)	24.0	5.4	0.1	3.9	1.7	0.2	0.1	17.4	12.4	1.9	7.7	0.4	46.6	a	a	97.8
	102.0 b	4.4	0.1	5.5	2.3	0.6	0.1	13.6	14.0	1.2	8.5	0.5	47.1	a	a	97.8
Group B	10.0	5.7	0.2	3.0	1.4	0.1	0.2	22.4	12.6	0.0	10.1	0.0	41.7	0.0	0.1	97.7
(3 ug/cm2)	24.0	4.7	0.2	3.8	1.8	0.3	0.1	15.7	13.0	1.4	10.1	0.4	44.0	0.2	0.1	96.0
	120.0	3.8	0.1	5.3	2.4	1.1	0.0	18.5	11.0	1.1	10.6	0.6	41.5	1.1	0.1	97.1
Group C	10.0	3.3	0.2	2.5	1.1	0.1	0.2	20.4	11.5	0.0	6.3	0.0	51.6	0.0	0.1	97.2
(0.3 ug/cm2)	24.0	4.5	0.2	3.9	1.7	0.3	0.2	13.9	12.4	1.9	13.2	0.4	44.0	0.6	0.0	97.2
	120.0	1.6	0.1	4.2	2.0	1.7	0.2	18.4	8.4	1.1	8.4	0.6	51.2	1.3	0.1	99.3

a Because of the low concentration in dose group B and C these samples were not analyzed.
b Shortened from 120 hours due to impending ice storm at the study site.
Col. 12. Corrections of % AD were made by the contract lab for fortified percent recovery of "charcoal filter #1" as follows: Group A = 92.9%, Group B = 89.8%, Group C = 88.6%.

Mean % AD of charcoal filter #2 was not corrected.

Table 3. Summary: Percent administered dose absorbed, unabsorbed and in dosed skin.

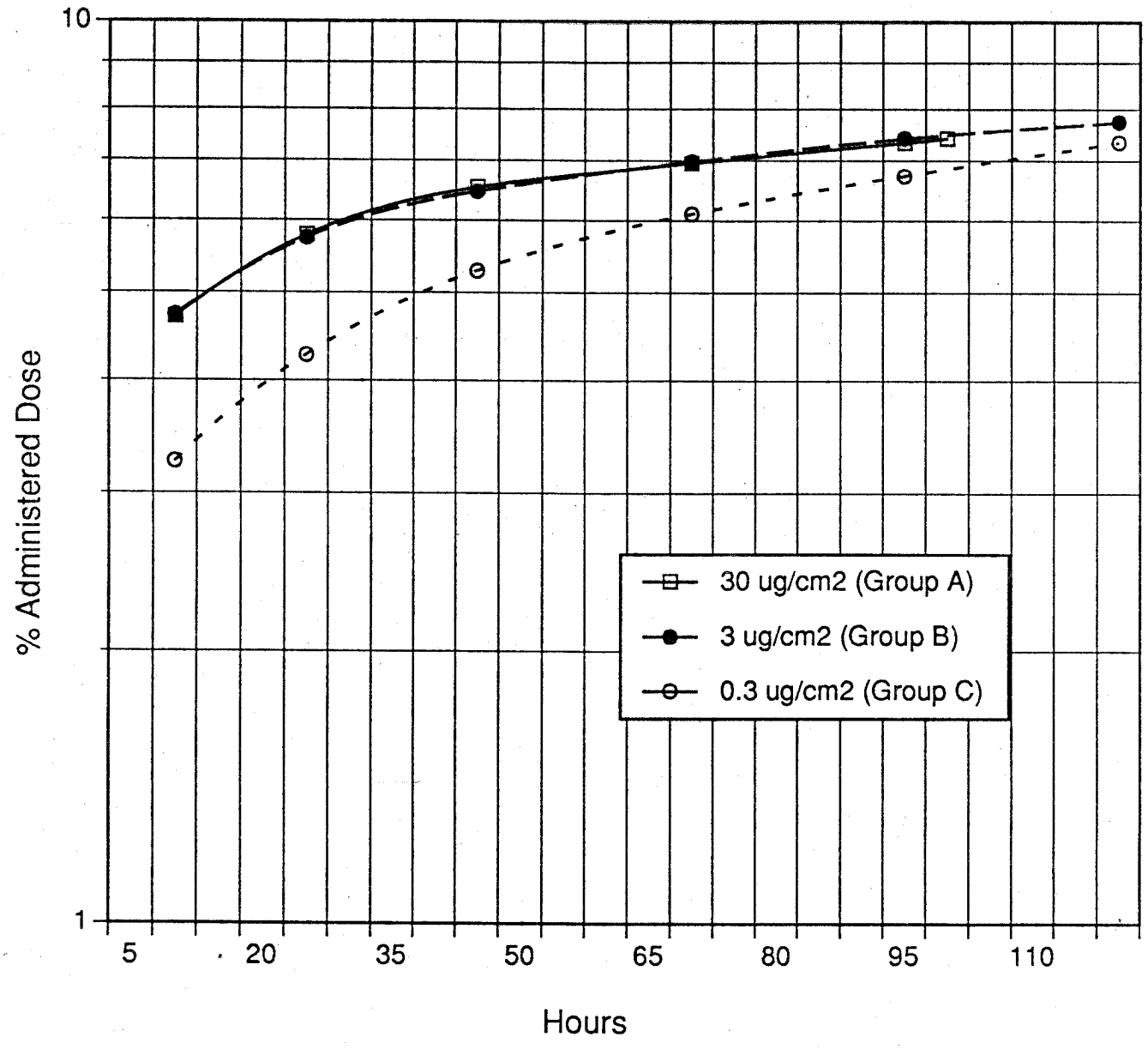
	Sacrifice time (h)	% Absorption	% Dose skin residues	% Unabsorbed dose	Total
Group A	10.0	13.3	22.5	61.2	96.9
(30 ug/cm^2)	24.0	11.4	17.4	69.1	97.8
	102.0	12.9	13.6	71.3	97.8
Group B	10.0	10.7	22.4	64.5	97.7
(3 ug/cm^2)	24.0	11.0	15.7	69.3	96.0
	120.0	12.7	18.5	65.9	97.1
Group C	10.0	7.3	20.4	69.5	97.2
(0.3 ug/cm^2)	24.0	10.8	13.9	72.5	97.2
	120.0	9.8	18.4	71.1	99.3

1. Percent absorption = Sum of % AD in columns 1-6 (Table 2).
2. Percent dosed skin residues = bound skin residues (column 7, Table 2).
3. Percent unabsorbed dose = Sum % AD shown in column 8-14 (Table 2).

Table 4. Summary: Percent dermal absorption of DDVP technical in male rats.

Sacrifice Time (h)	% AD ug/cm^2 30.0	3.0	0.3
10.0	13.3	10.7	7.3
24.0	11.4	11.0	10.8
120.0	12.9 (102 hours)	12.7	9.8

Fig. 1. Percent Administered Dose of ^{14}C-DDVP Recovered in Exhaled $C0_2$, Urine and Feces after Dermal Doses



M e m o r a n d u m

To : Bruce Bly, Registration Specialist
Pesticide Registration Branch

Date : October 25, 1990

Place: Sacramento

Via : John Ross, Senior Toxicologist
Worker Health and Safety Branch

Phone: 5-8474

From Department of Food and Agriculture - Tian Thongsinthusak, Staff Toxicologist
Worker Health and Safety Branch

Subject: PRODUCT NAME: Dormex
ACTIVE INGREDIENT: Hydrogen cyanamide
COMPANY NAME: SKW Trostberg AG
I.D. NUMBER: 125447-052
DOCUMENT NUMBER: 50660-052
EPA REGISTRATION NUMBER: 0-0-
TITLE: Dermal Absorption of ^{14}C-Hydrogen Cyanamide in Male Rats

Siemer & Associates, Inc. has submitted on behalf of SKW Trostberg AG a final report on a dermal absorption study of hydrogen cyanamide in male rats conducted by Hazleton Laboratories America, Inc. This document has been reviewed and evaluated by the Worker Health and Safety Branch concerning the percent dermal absorption and the acceptability of the study.

Four CRL:CD(SD)BR male rats (201-233 grams) were used for each sacrifice time, except for control and additional treatments with unlabeled hydrogen cyanamide. All rats were acclimatized and inspected by the performing laboratory. Prior to dose administration, hair on the application site (back and shoulders) was shaved and the shaved area was washed with acetone. The protective appliance (a plastic rectangle; 2.5 cm x 5 cm) was glued to the shaved area with a cyanoacrylate-based glue. Silicone medical adhesive, Type A, was used to seal around the outside of the enclosure. A non-occlusive pad (filter paper) was affixed to the plastic enclosure after dose administration.

Doses of hydrogen cyanamide used in this study were 0.1, 1.0, and 10.0 mg per rat equivalent to 8, 80, and 800 ug/cm^2. Non-labeled (Dormex 49% w/w aqueous solution) and ^{14}C-Iabeled hydrogen cyanamide (radiopurity 87-90% with a specific activity of 1.5 mCi/mmole) were mixed in deionized water. The dosing solution was adjusted to pH 4.5 with phosphoric acid. The pH adjustment was a means to stabilize the dosing solution and conformed to the product formulation where pH was adjusted to pH 4.6 with the same acid (1, 2). One hundred microliters of the dosing solution was administered to the 12.5 cm^2 of the shaved area with the aid of a glass rod spreader. All treated rats were individually housed in stainless steel metabolism cages which allowed separate collection of urine and feces. Each rat was supplied with water and Certified Rodent Chow #5002 ad libitum.

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The exposure times were 0. 5, 1, 2, 4, 10, and 24 hours. At the conclusion of the exposure period, rats were anesthetized with halothane and killed by exsanguination. The dosed skin site was excised from the animal. Five percent soap solution (Ivory liquid) and deionized water was used to wash dosed skin and plastic enclosure. A glass rod was used to gently agitate the dosed skin surface during the washing procedure. Samples collected for the analysis were: urine, feces, blood, carcass, dose cell cover, dosed skin and appliance washes, cage wipe, and washed skin.

All samples were prepared for analysis by liquid scintillation counter. Results were reported as percent of applied dose as shown in Table 1.

Table 1. Summary: Percent of applied dose recovered in various samples.

Exposure time (hours)	Samples	Mean % applied dose ----------mg/rat ---------- 0.1	1.0	10.0
	Penetrated dose[a]	0.07	0.16	0.12
0.5	Washed skin	6.57	4.41	7.47
	Unpenetrated dose[b]	98.23	98.60	90.69
	Total	104.87	103.17	98.28
	Penetrated dose[a]	0.19	0.29	0.66
1	Washed skin	6.80	4.03	11.70
	Unpenetrated dose[b]	90.53	94.33	84.35
	Total	97.52	98.65	96.71
	Penetrated dose[a]	0.13	0.69	0.91
2	Washed skin	7.48	8.67	9.46
	Unpenetrated dose[b]	90.58	88.20	86.39
	Total	98.19	97.56	96.76
	Penetrated dose[a]	0.27	0 . 5 3	1.85
4	Washed skin	6.48	5.99	5.33
	Unpenetrated dose[b]	91.52	91.62	79.07
	Total	98.27	98.14	86.25
	Penetrated dose[a]	1.20	2.64	7.53
10	Washed skin	7.03	6.81	6.81
	Unpenetrated dose[b]	90.34	85.50	78.3
	Total	98.57	94.95	92.64

Exposure time (hours)	Samples	Mean % applied dose ----------mg/rat---------- 0.1	1.0	10.0
24	Penetrated dose[a]	1.79	2.84	11.10
	Washed skin	17.00	13.50	11.10
	Unpenetrated dose[b]	75.40	76.63	67.23
	Total	94.19	92.97	89.43

[a] carcass, urine, feces, cage wipe
[b] protective appliance and skin washes, dose cell cover

From the results shown in the Table, penetrated dose of all dose groups increased with increasing dose levels and with increasing exposure times. In contrast, the percent of applied dose in washed skin (bound skin residues(was relatively stable at approximately 7 percent. The majority of the applied dose for all dose groups was recovered as unpenetrated dose (7 8.3 - 98.8 percent). Percent applied dose in blood was negligible and was not accounted for in dermal absorption estimates.

Bioavailability of bound skin residues of all dose groups cannot be determined because of the short observation times after a 10- or 24-hour exposure. The desirable observation time should be up to 1 week in order to evaluate the bioavailability of bound residues. From the avai1able data, it is appropriate to determine the mean percent dermal absorption by addition of percent penetrated dose and percent dose remaining in washed skin of all dose groups. These dose groups are expected to cover the range of worker exposure to hydrogen cyanamide. The mean percent dermal. absorption after correction for total dose recovery was determined to be 11.2 percent.

Recommendations:

1. This study is acceptable provided that dermal absorption of hydrogen cyanamide is determined by addition or percent penetrated dose and percent dose remaining in washed skin.

2. Dermal absorption of 11.2 percent will be used in. the Department's woke exposure estimates.

3. Dermal absorption may be reevaluated if the registrant elects to do a new dermal absorption study, but the study protocol must be approved by the Department.

References:

1. Request for an EUP to test Dormex on grapes as a plant growth regulator: Product chemistry. California Department of Food and Agriculture, *Registration Document* No. 50660-008.

2. Aero Cyanamide-50. Section 18 Emergency Exemption: Storage stability. California Department of Food and Agriculture, Registration Document No. 50660-010.

cc: Robert I. Krieger
Robert K. Brodberg
Joshua Johnson (1 original, 5 copies)